

## REMARKS

### **I. Status of Claims.**

Claims 1-13 are pending.

Claims are amended in a manner that is believed to overcome rejections contained in the pending Office Action. The amendments to the claims have been made solely for reasons of clarity. Support for these amendments can be found throughout the drawings, specification and claims as originally filed. No new matter or issues are believed to be introduced by these amendments.

### **II. Objection to Specification.**

**A. Abstract:** Objection was made to the abstract of the disclosure as containing more than one paragraph. Applicants have amended the abstract to comply with MPEPP 608.01(b). Applicants believe this objection has been met.

**B. Disclosure:** Objection was made to the disclosure by the Examiner as containing an embedded hyperlink and/or other form of browser-executable code. Applicants have amended the specification as set forth above removing these embedded hyperlinks. Applicants believe this objection has been met.

### **III. Claim Objection.**

The Examiner objected to claim 1 because of informalities in claim structure. Applicants have amended claim 1 as suggested by the Examiner. Applicants thank the Examiner for this suggested amendment and her diligence in examining the instant application.

### **IV. Rejection of claims 1, 3-6, 9 and 11-12 under 35 USC 112, first paragraph.**

In the Office Action dated January 27, 2003, the Examiner rejected claims 1, 3-6, 9 and 11-12 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner stated that the rejected claims are drawn to a method for modulating

behavioral and neurological adaptive responsiveness to stress by applying to the central nervous system a therapeutically effective amount of an inhibitor of the DP VI enzyme. The Examiner stated that the "instant specification fails to define any specific criteria, which clearly identify behavioral and neurological adaptive responsiveness to stress one would wish to modulate. Applicants respectfully traverse this rejection.

Applicants have provided numerous examples that contain dosing and criteria of evaluation of such dosing within various animals studies the results of which can be extrapolated for use in humans by those skilled in the art without undue experimentation. Applicants would direct Examiner's attention to the extensive criteria within Example 1-4 that more than fully comply with the requirements of 35 USC 112, first paragraph.

In Ex parte Chwang, 231 U.S.P.Q. 751 (P.T.O. Bd. App. and Interfer. 1986), another case which similarly presented claims for the treatment of mammals based upon animal tests, claims to compounds useful for the treatment of certain types of cancers in humans were rejected under §101 and §112 for an allegedly insufficient disclosure of utility. The only tests reported in the specification were *in vitro* and animal tests. The Examiner did not cite any specific problem about the tests, "with respect to their acceptance in the art as being predictive of efficacy in treating humans or in any other respect." Id. at 752. The Board concluded that the rejection must be reversed and that such showing was sufficient.

Applicants' situation is not like that of Ex parte Stevens, 16 U.S.P.Q.2d 1379, 1380, where the applicant had **no** evidence whatsoever, either *in vivo* or *in vitro*, to support the alleged utility of treating cancer. Rather, in the present application there is ample evidence of potential treatment utility based upon animal tests summarized in four examples. These examples provide a reasonable indication to one skilled in the art that the present invention would in fact have its asserted utility in Applicants' claimed method for the treatment of "the psychophysiological effects of stress".

Accordingly, it is respectfully submitted that the Patent Office has not provided the required reasonable basis for contending that one skilled in the art would not be able to practice the invention as claimed. Gould v. Mossinghoff 229 U.S.P.Q. 1, 13 (D.C. D.C. 1985).

In the alternative, if the Examiner is suggesting there is a basis for doubting Applicants' claimed method of treating the psychophysiological effects of stress including anxiety comprising the step of applying to the central nervous system a therapeutically effective amount of an inhibitor of dipeptidyl peptidase IV (DP IV) enzyme or of DP IV-like enzyme, the Examiner is respectfully requested to provide an affidavit under 37 C.F.R. § 107(b) required to support that position.

As to Claim 1, from which all pending claims depend, there is no basis for the Examiner's opinion of lack of enablement, as is required to maintain such a rejection. Gould v. Mossinghoff, 229 U.S.P.Q. 1, 13-14 (D.D.C. 1985) aff'd in part, vacate in part, and remanded sub nom, Gould v. Quigg, 3 U.S.P.Q. 2d 1302 (Fed. Cir. 1987)("In examining a patent application, the P.T.O. is required to assume that the specification complies with the enablement provision of section 112 unless it has 'acceptable evidence or reasoning' to suggest otherwise"; the burden of persuasion is on the P.T.O.); In re Armbruster, 185 U.S.P.O. 152 (C.C.P.A. 1975). The Examiner references neither the level of knowledge of "one of ordinary skill in the art," nor the nature of the impediments to enablement one might encounter. The Examiner is respectfully requested to provide an affidavit under §107(b) as to the reasoning under which enablement is questioned.

In the alternative, Applicants respectfully request that this rejection be withdrawn.

#### **V. Rejection of Claims 1-13 under 35 USC 112, second paragraph.**

The Examiner rejected claims 1-13 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of Applicants' invention.

A. The Examiner rejected claim 1 for the indefinite use of an acronym, "DP IV" without providing a full name at the first appearance of the term. Applicants have amended claim 1 as Examiner has suggested. Applicants respectfully submit that this rejection has been overcome.

B. Claim 1 was further rejected under 35 USC 112, second paragraph for recitation of "modulating behavioral and neurological adaptive responsiveness." Applicants have amended claim 1 to clearly define the instant claimed invention. Applicants respectfully submit that this rejection has been overcome.

C. The Examiner also rejected claim 1 under 35 USC 112, second paragraph for recitation of "brain or central nervous system." The Examiner suggested that use of the two terms was confusing. Applicants have amended claim 1 deleting reference to "brain." Applicants thank the Examiner for this suggested amendment. In light of this amendment, Applicants respectfully submit that this rejection has also been overcome.

D. Claims 1 and 2 were rejected under 35 USC 112, second paragraph for the term DP IV -like enzyme. The Examiner stated that it was not obvious, which enzymes are to be included or excluded by the limitation "like." Applicants respectfully traverse this rejection.

Claims 1 and 2 are directed to DP IV and DP IV-like enzymes. One skilled in the art would clearly understand that the 'like' enzymes would be those enzymes having identical or similar enzymatic activity as that of the dipeptidyl peptidase IV enzyme. Most particularly, Examiner's attention is drawn to page 20 lines 27-35 discussing DP-IV "like" enzyme activity. It is clear from the instant specification that DP-IV "like" enzyme activity is understood to mean where such inhibition will result in a reduction or delay in the decrease of the concentration of functionally active NPY (1-36). Applicants further draw the Examiner's attention to page 10 lines 24-29 of the instant application where the suffix 'like' is used in the context of anxiolytic like effects. It is clear from this context that "like" means generally the same as. Similarly, the Examiner's attention is drawn to page 12 lines 25-29 where anti-epileptic "like" drugs are discussed; and to page 12 line 35 continuing to page 13 line 8 and lines 19-24 addressing NPY

“like” –immunoreactivity. The Examiner’s attention is further drawn to the plain dictionary meaning of “like” which is defined as “having the characteristics of; similar to or typical of” (Webster’s Ninth New Collegiate Dictionary 1988). It is clear from these passages and the plain dictionary meaning, that one skilled in the art would accept these as commonly used terms and would understand the metes and bound of Applicants’ invention. Applicants respectfully request that this rejection be withdrawn.

E. Further rejection was made to claim 2 for the recitation of “other substrates sharing similar properties.” The Examiner stated that it was not clear what “other substrates” were intended by the claim. The Examiner also rejected claim 2 as the acronym CD26 was used instead of its full name. Applicants have amended claim 2 to clearly define their invention. Applicants respectfully submit that this rejection is met.

F. The Examiner also rejected claims 3-5 and 7-8 for improper antecedent basis for “inhibitors”. Applicants have amended the claims to correct this and respectfully submit that this rejection has been overcome as well.

G. Claims 4 and 7 were rejected for the recitation of “ will be present”. The Examiner stated that using future tense in the text of the claims implies future limitations rendering the claim language indefinite. Applicants have amended claims 4 and 7 to remove the future tense and respectfully submit that this rejection may be properly withdrawn.

H. Further rejection was made to claims 6 and 10-13 for reciting the limitation of “DP IV inhibitors” in claims 1, 2 and 4 without sufficient antecedent basis for this limitation. Applicants have amended these claims and respectfully submit that this rejection may also be properly withdrawn.

I. The Examiner also rejected claim 9 as being indefinite for being dependent from an indefinite claim. Applicants have amended claim 8 from which claim 9 depends and respectfully submit that this rejection is overcome.

**VI. Rejection of claims 2, 7-8, 10 and 13 under 35 USC 102(b).**

The Examiner rejected claims 2, 7-8, 10 and 13 under 35 USC 102(b) as being anticipated by Powers et al. (WO 95/2961, 1995, Document BL, IDS of Paper No. 2) (“Powers”). Applicants respectfully traverse this rejection.

**A. Examiner’s Rejection:** The Examiner’ rejection stated that Powers discloses inhibitors of dipeptidyl peptidase IV and their use of administration as anti-inflammatory agents, anticoagulants, anti-tumor agents and anti-AIDS agents. Administration of therapeutic amounts of inhibitors of Powers leads to the decrease of enzymatic activity of DPIV and consequently to the reduction of degradation of its natural endogenous substrate.

**B. Applicants’ Claimed Invention:** Applicants’ claimed invention as found in claim 1, from which all subsequent claims depend, is directed to the “treatment of psychophysiological effects of stress” resulting from central nervous system disorders such as anxiety. Applicants claimed method of treating central nervous system disorders such as anxiety is by the administration of DP-IV inhibitors.

**C. Teachings of Powers:** Power discloses the use of peptidyl derivative of diesters of  $\alpha$ -aminoalkylphosphonic acids, particularly those with proline or related structures, their use in inhibiting serine proteases with chymotrypsin-like, elastase-like, and dipeptidyl peptidase IV specificity. The disclosure of Powers is directed to the use of these compounds as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents.

**D. Deficiencies of Powers:** Claim 1 from, which all pending claims depend, is directed to the “treatment of psychophysiological effects of stress” resulting from central nervous system disorders such as anxiety. Unlike Applicants’ claimed invention, Powers is completely devoid of any disclosure teaching or making obvious the use of DP-IV inhibitors for the treatment of central nervous system disorders. Applicants respectfully request that this rejection be withdrawn.

**VII Rejection of claims 1-13 under 35 USC 102(b).**

The Examiner rejected claims 1-13 under 35 USC 102(b) as being anticipated by Powers et al. (WO 95/2961, 1995, Document BL, IDS of Paper No. 2) ("Powers") in view of WO 97/40832 (Demuth '832) and Lader, 1981 (Lader). The combination of references makes this rejection under 35 USC 102(b) improper. As has been clearly enunciated by the Federal Circuit: Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. Lindermann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 221 USPQ 481, 485 (Fed Cir. 1984) (emphasis added). Here the requirement of showing each and every element of Applicant's claimed invention in a single prior art reference has not been met, as Powers alone or even in combination with the other references, fails to disclose or teach Applicants' claimed invention. It is respectfully requested that these improper rejections under 35 U.S.C. §102(b) be withdrawn.

Applicants, in the interest of moving the instant case to allowance, treat this rejection as if it was based upon an obviousness type rejection under 35 USC 103(a). On this basis, applicants traverse the above rejection of claims 1-13.

**A. Examiner's Rejection:** The Examiner's rejection stated that Powers discloses inhibitors of dipeptidyl peptidase IV and their use of administration as anti-inflammatory agents, anticoagulants, anti-tumor agents and anti-AIDS agents. Administration of a therapeutic amount of inhibitors of Powers leads to the decrease of enzymatic activity of DPIV and consequently to the reduction of degradation of its natural endogenous substrate. As such, the administration of DPIV inhibitors as disclosed by Powers leads to reduction in stress responsiveness and anxiety. The examiner further stated that this is especially true in view of art recognition of use of DPIV inhibitors to alter blood sugar levels as disclosed in Demuth '832 and close association of anxiety and abnormal concentration of blood glucose as disclosed in Lader. The Examiner speculated that one would reasonably expect that administration of a DPIV inhibitor to treat inflammation, AIDS and blood coagulation as disclosed by Powers or to alter blood sugar levels as disclosed in Demuth '832, a syndrome closely associated with anxiety would lead to therapy of anxiety and reduction of stress responsiveness, as disclosed in the instant specification.

**B. Applicants' Claimed Invention:** Applicants' claimed invention as set forth in claim 1, from which all subsequent claims depend, is directed to the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety. Applicants' claimed invention is directed to the beneficial neurological and psychophysiological effects that result from the inhibition of DP-IV-like enzymatic activity within the central nervous system by the administration of DP-IV inhibitors.

**C. Teachings of Powers:** Power discloses the use of peptidyl derivative of diesters of  $\alpha$ -aminoalkylphosphonic acids, particularly those with proline or related structures, their use in inhibiting serine proteases with chymotrypsin-like, elastase-like, and dipeptidyl peptidase IV specificity and their roles as anti-inflammatory agents, anticoagulants, anti-tumor agents, and anti-AIDS agents.

**D. Teachings of Demuth '832:** Demuth '832 discloses the action of DP IV effectors to increase the stability of incretins or analogues thereof which are available endogenously or exogenously which then provided for increased levels for insulinotropic stimulation of the incretin receptors of the Langerhans cells in the pancreas, thereby also changing the power of endogenous insulin in turn stimulating the metabolism of carbohydrates in the treated organism. As a result, the blood sugar level drops below the glucose concentration characteristic of hyperglycaemia.

**E. Teachings of Lader:** Lader discloses that life events are important determinants of the severity of anxiety responses and that a standardized Life Events Schedule is a useful instrument to have available. The relationship between the occurrence of one or more life events and clinical response to each treatment can then be assessed.

**F. Deficiencies of Cited References:** Unlike Applicants' claimed invention, none of the cited reference, either alone or in combination disclose or suggest the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety using an inhibitor of DP IV. None of the three cited references, whether taken alone or in combination, arrive at the subject matter of Applicants' claimed invention.

Since the claimed combination is not found in the art, it is fair to assume that in raising the obviousness rejection, the Examiner gleaned knowledge from Applicants' disclosure,



contrary to well-established legal principles. Applicants respectfully request that the rejected claims be favorably reconsidered in light of well-established legal principles, which provide,

*"That one skilled in the art is not synonymous with obviousness.... That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the reference to make the claimed invention" Ex parte Levengood, 28 USPQ 2d 1300 (Bd. Pat. App. & Inter. 1993).*

The combination of the cited references is neither taught nor suggested by either reference. The references, alone or in combination, as discussed above, do not provide "sufficient impetus" to support the combination that the Examiner makes to effect the obviousness rejection. Only applicants' own disclosure could provide this motivation and that is an improper use of applicants' specification. In any event, it is respectfully submitted the suggested combination fails to teach or make obvious Applicants' invention.

#### **VII. Rejection of claims 1-13 under 35 USC 102(e).**

The Examiner rejected claims 1-13 under 35 USC 102(e) as being anticipated by Demuth et al., U.S. Patent No. 6,319,893 (Demuth '893). Applicants respectfully traverse this rejection.

**A. Examiner's Rejection:** The Examiner stated that Demuth '893 describes the administration to a mammal of therapeutically effective amounts of an inhibitor of DPIV. The Examiner further stated that Demuth '893 also discloses methods of administration (parenterally, orally), pure forms of inhibitors and in formulations with physiologically acceptable adjuvants.

**B. Applicants' Claimed Invention:** Applicants' claimed invention as set forth in claim 1, from which all subsequent claims depend, is directed to the "treatment of psychophysiological effects of stress" resulting from central nervous system disorders such as anxiety. The instant claims are directed to methods of treating these central nervous system disorders such as anxiety by the administration of DP-IV inhibitors.

**C. Teachings of Demuth '893:** Demuth '893 discloses a method of raising the blood sugar level in a mammal having hypoglycemia. The method disclosed in Demuth '893 reduces degradation of glucagons by administering to the mammal a therapeutically effective amount of an inhibitor of dipeptidyl peptidase IV and physiologically acceptable adjuvants and/or excipients.

**D. Deficiencies of Demuth '893:** Demuth '893 is completely devoid of any disclosure suggesting the use of DP-IV inhibitors for the treatment of central nervous system disorders. Applicants respectfully request that this rejection be withdrawn.

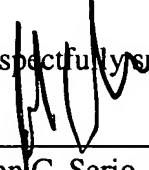
#### **VIII. Rejection of claims 1-13 under Obviousness-type Double Patenting.**

A rejection was made to claims 1-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,319,893 (Demuth '893). Applicants respectfully but vigorously suggest that the claimed subject matter of the rejected claims differ from that of the claims of Demuth '893, as discussed immediately above. Specifically, claims 1-13 are directed to methods of treatment of central nervous system disorders, while Demuth '893 discloses a "method of raising the blood sugar level in a mammal having hypoglycemia by reducing degradation of glucagons." These are neither the same nor obvious from one another. Applicants respectfully request that this rejection be withdrawn.

### CONCLUSION

The claims remaining within the application are believed to patentably distinguish over the prior art and to be in condition for allowance. Early and favorable consideration of this application is respectfully requested.

Respectfully submitted,



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